REMARKS

Claim Status

Claims 1-26, 28, and 29 are pending in the present application.

Claim 1 is amended to characterize a select embodiment. Support may be found on page 6, line 30 to page 7, line 16 of the specification.

Claim 21 is amended to more clearly characterize an embodiment. Support may be found on page 6 of the specification.

Claims 23 and 24 are amended to retain proper antecedent basis.

Claims 6-20 have been withdrawn as a result of an earlier restriction requirement.

Claims 30-36 are new. Support for claim 30 may be found on page 29 of the specification. Support for claims 31-36 may be found on pages 7-10 of the specification.

These changes do not involve any introduction of new matter. Consequently, entry of these changes is respectfully requested. No additional claims fee is believed to be due.

Response to Double Patenting Rejection

Claims 1-3 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of copending Application No. 10/152,924 Since the rejection is provisional based upon an application, Applicant requests that the rejection be held in abeyance until such time that Application No. 10/152,924 is allowed and issues as a patent.

Rejection Under 35 USC §103(a)

Claims 1-5, 21, 23-24, 265 and 28-29 are rejected under 35 USC § 103(a) over U.S. Patent No. 6,284,802 to Bissett et al. ("Bissett"). In support for the rejection, the Office states:

> Bissett et. al. discloses the use of vitamin B3 compounds in skin care compositions. (Column 33, claim 3). Example 1 discloses a composition with 2% niacinamide, a vitamin B3 compound. (Column 30, lines 1-5; Column 16-17, section titled "Vitamin B3 compounds"). Water, glycerin and silicone fluids are disclosed in emulsions and are considered carriers. (Example 2). Hexamidine is disclosed as useful as an antimicrobial adduct. (Column 23, line 45-55).

The Office concedes that "Bissett does not exemplify a composition comprising hexamidine." The Office concludes that "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a skin care composition comprising hexamidine, and

vitamin B3 and additional ingredients such as peptides, additives claimed in claim 3, and tocopherol acetate since all ingredients are well known for their use in skin care preparations and useful for compositions for skin care as disclosed in Bissett et. al." Applicant traverses the rejection.

The Office argues that "the combination [of hexamidine and vitamin B3] would have yielded predictable results to one of ordinary skill in the art at the time of the invention." Applicant submits that the combination of hexamidine and vitamin B_3 yields unexpected and unappreciated results related to the regulation of mammalian keratinous tissue. In support of this assertion, attached is a declaration submitted under 37 C.F.R. §1.132 from Rosemarie Osborne, Ph.D. Dr. Osborne is an expert in the field of *in vitro* testing. Dr. Osborne examined the effect of hexamidine and niacinamide with an *in vitro* model of human skin. Specifically, the effect of hexamidine and niacinamide on gene expression was investigated. The value of investigating gene expression is that many of the genes showing changes in expression can be linked to biological processes that may serve to improve the condition and appearance of keratinous tissue such as the skin. *In vitro* testing is ideal for comparative analysis studies, in part, because it detects the fundamental ways that skin responds to a treatment, and allows for greater control of the test subject and less variability as compared to *in vivo* testing.

While specifics are more thoroughly described in the declaration, provided herein is a summary of the experiment and of the unexpected results. The experiment involved topically treating the *in vitro* skin samples with a water control, hexamidine, niacinamide, and the combination of hexamidine and niacinamide. After the treatment period, the mRNA was isolated from the epidermal layer of the *in vitro* skin samples. The epidermal mRNA was analyzed using a commercially available process and device, GeneChip microarray available from Affymetrix, Inc. The GeneChip can detect thousands of mRNA transcripts many of which are derived from genes that are known to regulate a biological function. The gene expression (through the detection of mRNA transcripts) of an experimental composition can be compared with the gene expression of a control to determine if the experimental composition is affecting particular genes. In many cases, the affected genes can be grouped into themes where the specific biological functions of the genes are known.

Dr. Osborne found that more than 300 genes in the epidermis showed statistically significant synergistic expression. *Declaration, page 8, first paragraph.* The synergistic effects met two notable criteria. First, the synergistic effects are statistically significant. The 300 genes reported in the declaration show a statistically significant synergistic expression of $p < 0.05$

based on analysis of variance modeling. *Declaration, page 7, second paragraph.* For many genes, the synergistic effect showed a greater statistical significance of $p \leq 0.001$, $p \leq 0.0001$, or $p \leq 0.00001$. *Declaration, Table 3.* Second, the 300 genes reported in the declaration exhibit a substantial synergy The 300 genes reported exhibit a synergistic effect of at least 30% greater (*i.e.*, 1.3 times greater) than what would have been predicted by the additive effect alone. *Declaration, page 6, first paragraph.* The synergy requirement in Dr. Osborne's research is far more stringent than a mere *de minimus* synergy where the increase over the predicted additive effect is a marginal. Many of the reported genes show a synergistic effect more than 3-times greater than the predicted additive effect of hexamidine and a vitamin B_3 compound. The magnitude of the synergy is unanticipated and profound. *Declaration, page 8, first paragraph.*

Another important result of the Dr. Osborne's work is correlation of synergistic genes to biological pathways. *Declaration, Table 3 and page 9, paragraph 1.* The 300 genes showing synergistic expression were not random in their biological process impact. Dr. Osborne found that many of the genes showing synergy with the application of hexamidine and niacinamide compared to the additive effect of hexamidine and niacinamide relate to specific biological pathways. For example, the biological process of gluconeogenesis (*i.e.*, the generation of glucose from non-sugar carbon substrates) showed a synergistic up-regulation (*i.e.*, increase in mRNA transcripts triggering gluconeogenesis). *Declaration, page 9, second paragraph.* The up-regulation of genes related to gluconeogenesis was found to have a very high degree of statistical significance ($p \leq 0.0001$). As described by Dr. Osborne, an increase of glucose is fundamental to processes for regulating the condition of mammalian keratinous tissues such as skin (*e.g.*, preventing, retarding, and/or treating skin conditions including the appearance of fine lines and/or wrinkles; hyperpigmentation such as post-inflammatory hyperpigmentation; sagging; skin atrophy; skin dryness; dark under-eye circles and puffy eyes; sallowness; desquamating, exfoliating, and/or increasing skin turnover; enlarged pores; and/or oily and/or shiny appearance of skin).

Delving even deeper into the work performed, Dr. Osborne points to a particular gene involved in gluconeogenesis, triose phosphate isomerase. *Declaration, page 10, first paragraph.* As can be seen in the graph provided on page 10 of the declaration, hexamidine did not affect gene expression in relation to the control. Niacinamide produced a 70% increase in the mRNA related to the expression of triose phosphate isomerase. Surprisingly, the combination of niacinamide and hexamidine increased triose phosphate isomerase expression by 260% of the

control ($p = 0.047$ with significance set at $p < 0.05$). This is one of many genes showing a 3-fold increase in expression over predicted additive effect of niacinamide and hexamidine.

Synergistic effects of niacinamide and hexamidine were also shown in relation to cellular protein formation. *Declaration, page 10, second paragraph.* Dr. Osborne found that niacinamide and hexamidine up-regulated genes involved in RNA splicing, which is responsible for "editing" RNA to produce mature mRNA which, in turn, is the template for protein synthesis. Additionally, niacinamide and hexamidine were found to down-regulate genes involved in protein catabolic processes, which is the process of breaking-down proteins. The surprising discovery is that niacinamide and hexamidine are synergistically affecting protein formation, via two distinct routes. By up-regulating genes involved in RNA splicing, proteins may be readily produced by having ample mature mRNA available. By down-regulating genes involved in protein catabolism, existing proteins are stabilized and have a longer duration in the cells before eventual break-down. The two protein routes are fundamental to processes that regulate the condition of mammalian keratinous tissues and provide skin structural protein changes essential toward preventing, retarding, and/or treating skin conditions such as the appearance of fine lines and/or wrinkles; sagging; skin atrophy; skin dryness; desquamating, exfoliating, and/or increasing skin turnover; and regulating and/or reducing the size of pores. It must be emphasized that the synergistic effect of niacinamide and hexamidine on mRNA splicing taken alone or protein catabolism taken alone is surprising. It is all the more unexpected that niacinamide and hexamidine synergistically affect separate pathways that impact cellular proteins which serve as essential building blocks for regulation of keratinous tissues.

The Office is encouraged to contact the Applicant's representative if any questions arise regarding the declaration. However, in light of the comments presented above and the declaration submitted hereto, Applicant asserts that the claimed invention is patentably distinct over the cited reference. The declaration evidences the unexpected results originating from the combination of hexamidine and a vitamin B_3 compound. The data provided demonstrates a statistically significant and substantial synergistic effect. Therefore, Applicant respectfully requests withdrawal of the rejection and allowance of the pending claims.

Claims 1-5, 23, 26-29 are rejected under 35 USC §103(a) over U.S. Patent No. 6,589,514 (hereinafter "Jensen") in view of Flick et al. ("Flick")(Cosmetic Additives – An Industrial Guide, Pages 647-648, 652; PTO-892) further in view of Gensler et al. ("Gensler")(Nutrition and Cancer, 29(2), 157-162; PTO-892), and JP2002212053 to Oblong et al. ("Oblong"). In light of

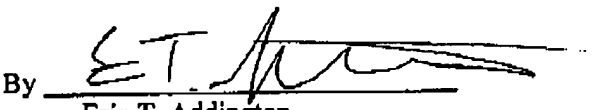
the discussion presented above in regard to Bissett and the declaration submitted hereto, Applicant asserts that the claimed is patentably distinct over the combination of cited references. The declaration evidences the unexpected results originating from the combination of hexamidine and a vitamin B_3 compound. The data provided demonstrates a statistically significant and substantial synergistic effect. Therefore, Applicant respectfully requests withdrawal of the rejection and allowance of the pending claims.

CONCLUSION

This response represents an earnest effort to place the present application in proper form and to distinguish the invention as claimed from the applied reference(s). In view of the foregoing, it is requested that the Examiner reconsider and withdraw the rejections. Early and favorable action in the case is respectfully requested. Again, the Office is encouraged to contact the Applicant's representative should questions arise regarding this correspondence or the attached declaration.

Respectfully submitted,

THE PROCTER & GAMBLE COMPANY

By 

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